

Appl. No. 09/865,989
Amdt. dated September 10, 2003
Reply to Office Action of July 11, 2003

II. Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1-75. (Cancelled)

76. (Currently amended) An ApoA-I agonist compound comprising:

(i) an 18 to 22-residue peptide or peptide analogue which forms an amphipathic α -helix in the presence of lipids and which comprises formula (I):

$Z_1-X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-Z_2$

or a pharmaceutically acceptable salt thereof, wherein

X_1 is Pro (P), Ala (A), Gly (G), Asn (N), Gln (Q) or D-pro (p);

X_2 is an aliphatic residue;

X_3 is Leu (L);

X_4 is an acidic residue;

X_5 is Leu (L) or Phe (F);

X_6 is Leu (L) or Phe (F);

X_7 is a basic residue;

X_8 is an acidic residue;

X_9 is Leu (L) or Trp (W);

X_{10} is Leu (L) or Trp (W);

X_{11} is an acidic residue or Asn (N);

X_{12} is an acidic residue;

X_{13} is Leu (L), Trp (W) or Phe (F);

X_{14} is a basic residue or Leu (L);

X_{15} is Gln (Q) or Asn (N);

X_{16} is a basic residue;

X_{17} is Leu (L);

X_{18} is a basic residue;

wherein at least one L-enantiomeric residue of [the peptide or peptide analogue]

formula (I) is [[a]] replaced with an identical D-enantiomeric residue;

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Z_1 is H_2N- , or $RC(O)NR-$;

Z_2 is $-C(O)NRR$, $-C(O)OR$ or $-C(O)OH$;

each R is independently $-H$, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 4-residue peptide or peptide analogue in which one or more bonds between residues 1 through 4 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each “-” between residues X_1 through X_{18} independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic;

(ii) a 14 to 21-residue deleted peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} and X_{18} are optionally deleted and wherein at least one remaining L-enantiomeric residue of [the deleted peptide or peptide analogue] formula I is replaced with an identical [[a]] D-enantiomeric residue; or

(iii) an 18 to 22-residue altered peptide or peptide analogue according to formula (I) in which at least one of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} and X_{18} is conservatively substituted and wherein at least one L-enantiomeric residue of the resulting altered peptide or peptide analogue is replaced with an identical [[a]] D-enantiomeric residue; or

an N-terminally blocked form, a C-terminally blocked form or an N- and C-terminally blocked form of formula (I).

77. (Canceled)

78. (Previously presented) The ApoA-I agonist compound of Claim 76 which is the altered peptide or peptide analogue according to formula (I).

79. (Previously presented) The ApoA-I agonist compound of Claim 76 which is the deleted peptide or peptide analogue according to formula (I).

80. (Previously presented) The ApoA-I agonist compound of Claim 79 in which one or two helical turns of the peptide or peptide analogue is optionally deleted.

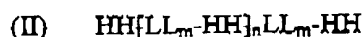
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81. (Previously presented) The ApoA-I agonist compound of Claim 76 which is an 18-residue peptide or peptide analogue according to formula (I).

82. (Previously presented) The ApoA-I agonist compound of Claim 81 in which
the "-" between residues designates -C(O)NH-;
Z₁ is H₂N-; and
Z₂ is -C(O)OH or a salt thereof.

83. (Previously presented) The ApoA-I agonist compound of Claim 82 in which;
X₁ is Ala (A), Gly (G), Asn (N) or Pro (P);
X₂ is Ala (A), Val (V) or Leu (L);
X₃ is Leu (L);
X₄ is Asp (D) or Glu (E);
X₅ is Leu (L) or Phe (F);
X₆ is Leu (L) or Phe (F);
X₇ is Arg (R), Lys (K) or Orn;
X₈ is Asp (D) or Glu (E);
X₉ is Leu (L) or Trp (W);
X₁₀ is Leu (L) or Trp (W);
X₁₁ is Glu (E) or Asn (N);
X₁₂ is Glu (E);
X₁₃ is Leu (L), Trp (W) or Phe (F);
X₁₄ is Arg (R), Lys (K) or Orn;
X₁₅ is Gln (Q) or Asn (N);
X₁₆ is Arg (R), Lys (K) or Orn;
X₁₇ is Leu (L); and
X₁₈ is Arg (R), Lys (K) or Orn.

84. (Currently amended) A multimeric ApoA-I agonist compound which comprises formula (II):



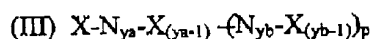
or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

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n is an integer from 0 to 10;
 each "HH" is independently a peptide or peptide analogue according to Claim [[1]] 76, the deleted peptide or peptide analogue according to Claim [[1]] 76 or the altered peptide or peptide analogue according to Claim [[1]] 76;
 each "LL" is independently a bifunctional linker; and
 each "-" independently designates a covalent linkage; or
 an N-terminally blocked form, a C-terminally blocked form or an N- and C-terminally blocked form of formula (II).

85. (Currently amended) A multimeric ApoA-I agonist compound which comprises formula (III):

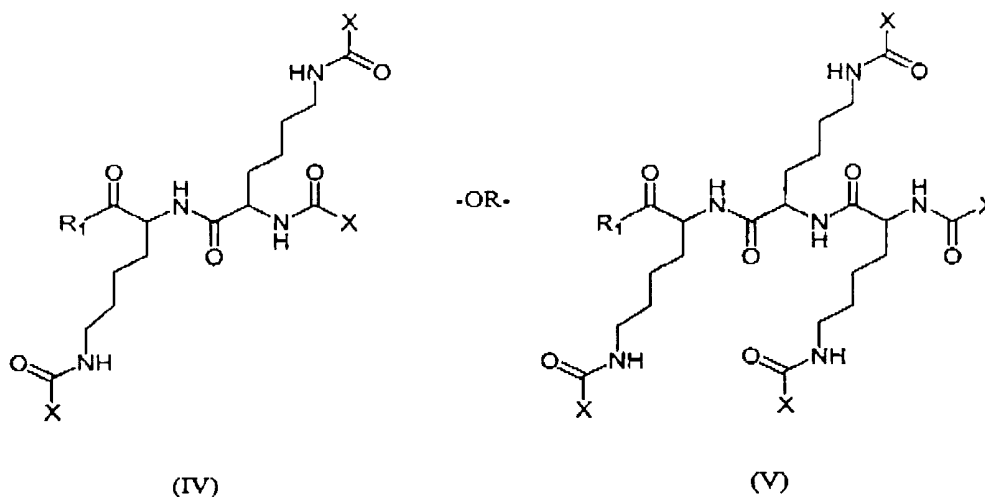


or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $[(HHLL_m-HH_nLL_m-HH)] \underline{HH[LL_m-HH]_nLL_m-HH}$;
 each HH is independently a peptide or peptide analogue according to Claim [[1]] 76, the deleted peptide or peptide analogue according to Claim [[1]] 76 or the altered peptide or peptide analogue according to Claim [[1]] 76;
 each LL is independently a bifunctional linker;
 each m is independently an integer from 0 to 1;
 each n is independently an integer from 0 to 8;
 N_{y_a} and N_{y_b} are each independently a multifunctional linking moiety where y_a and y_b represent the number of functional groups on N_{y_a} and N_{y_b} , respectively;
 each y_a or y_b is independently an integer from 3 to 8;
 p is an integer from 0 to 7; and
 each "-" independently designates a covalent bond; or
 an N-terminally blocked form, a C-terminally blocked form or an N- and C-terminally blocked form of formula (III).

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86. (Currently amended) A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $[[\text{HHLL}_m\text{--HH}_n\text{LL}_m\text{--HH}]] \text{ HHFL}_m\text{--HH}_n\text{LL}_m\text{--HH}$;

each HH is independently a peptide or peptide analogue according to Claim [[1]] 76,

the deleted peptide or peptide analogue according to Claim [[1]] 76 or the altered peptide or peptide analogue according to Claim [[1]] 76;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R₁ is -OR or -NRR; and

each R is independently -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; or

an N-terminally blocked form or a C-terminally blocked form of formula (IV) or (V).

87. (Previously presented) The multimeric ApoA-I agonist compound of Claim 84, 85 or 86 in which the bifunctional linker is cleavable.

88. (Previously presented) The multimeric ApoA-I agonist compound of Claim 84, 85 or 86 in which n is 0.

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89. (Previously presented) The multimeric ApoA-I agonist compound of Claim 86 in which m is 0.
90. (Previously presented) The multimeric ApoA-I agonist compound of Claim 84, 85 or 86 in which each HH is independently an altered peptide or peptide analogue.
91. (Previously presented) The multimeric ApoA-I agonist compound of Claim 84, 85, or 86 in which each HH is independently a deleted peptide or peptide analogue.
92. (Previously presented) An ApoA-I agonist compound-lipid complex comprising a lipid and an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.
93. (Previously presented) The ApoA-I agonist compound-lipid complex of Claim 92 in which the lipid is sphingomyelin.
94. (Previously presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient or diluent and an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.
95. (Previously presented) A pharmaceutical composition comprising an ApoA-I agonist compound-lipid complex wherein the ApoA-I agonist compound-lipid complex is comprised of an ApoA-I agonist compound according to Claim 76, 84, 85 or 86, a lipid and a pharmaceutically acceptable carrier, excipient or diluent.
96. (Previously presented) The pharmaceutical composition of Claim 95 in which the lipid is sphingomyelin.
97. (Previously presented) The pharmaceutical composition of Claim 96 which is a lyophilized powder.
98. (Previously presented) A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.

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99. (Previously presented) A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.

100. (Previously presented) The method of Claim 98 in which said subject is a human.

101. (Previously presented) The method of Claim 99 in which said subject is a human.

102. (Previously presented) The method of Claim 98 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist compound is administered to said subject.

103. (Previously presented) The method of Claim 99 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist compound is administered to said subject